


Models, Mice, and Men:

Diversifying the Portfolio

Charles Keller, MD
Children's Cancer Research Institute
University of Texas Health Science Center
at San Antonio



What role do live animal models have in personalized medicine?

Children's Cancer Research Institute
University of Texas Health Science Center
at San Antonio

Numira Biosciences


**Legislated mandate:
Cure Childhood Cancer
\$200M endowment**

**VISUAL
INFLUENCE INC.**


www.sarcomalab.org

www.numirabio.com
www.visual-influence.com

The Clinical Challenge



Non-Resectable



Metastatic

Courtesy of Keith White, MD (PCMC)

**100 years of modern science
why can't we cure cancer?**

Koch's Postulates, 1890

Tumor cells

Stromal cells

Immune cells

Vessels

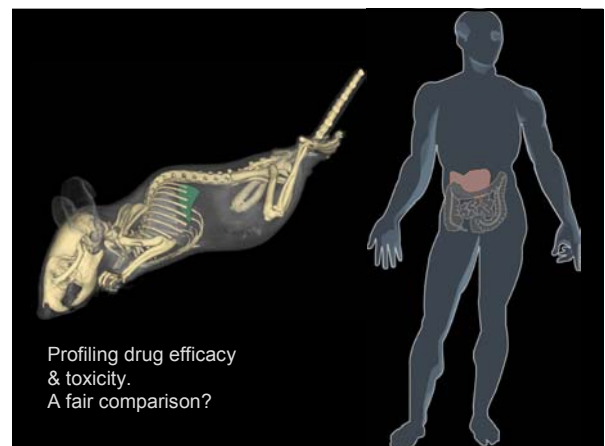
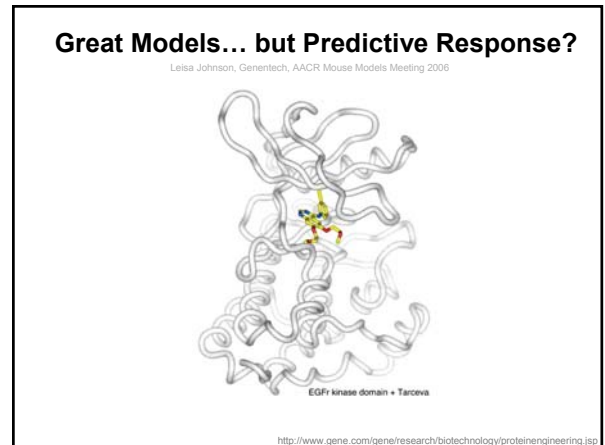
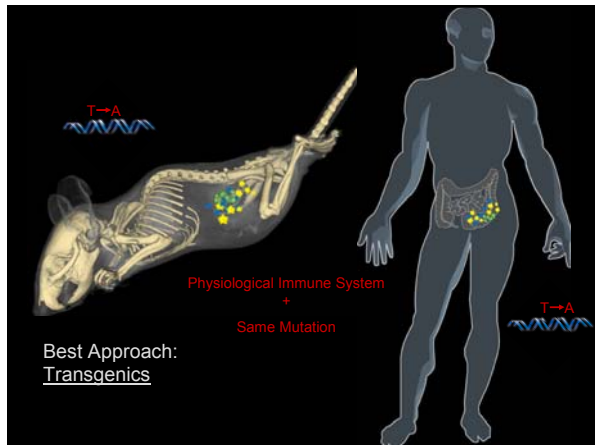
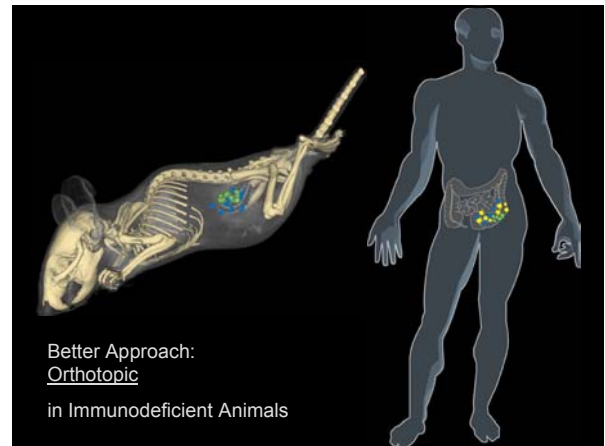
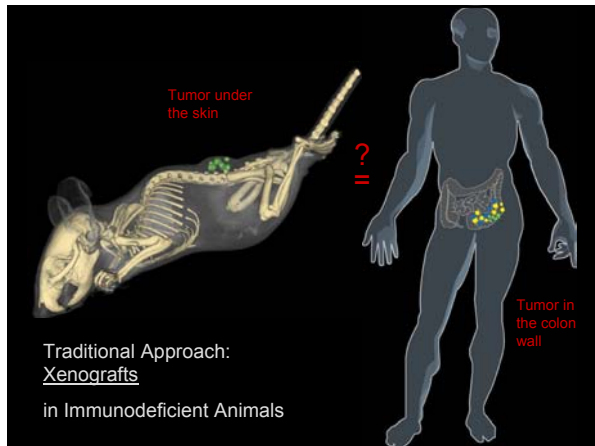
Diseased cells have important interaction with non-diseased cells

Infiltrating neutrophils mediate the initial angiogenic switch in a mouse model of multistage carcinogenesis

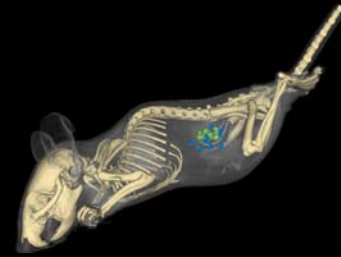
Wondol ResearchSM, Christopher ChouSM, and Douglas BonfieldSM
Research and Development Center, Children's Cancer Research Institute, University of California, San Francisco, CA 94143

Mouse vs. Man

Creating a Fair Comparison



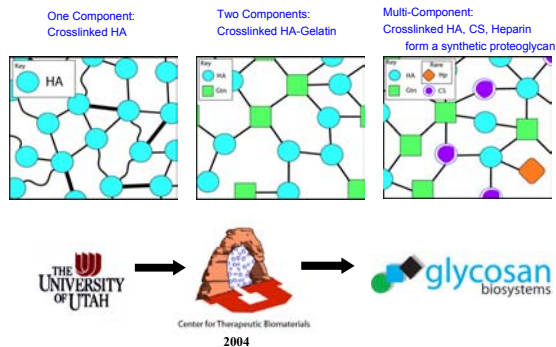
where are the opportunities?



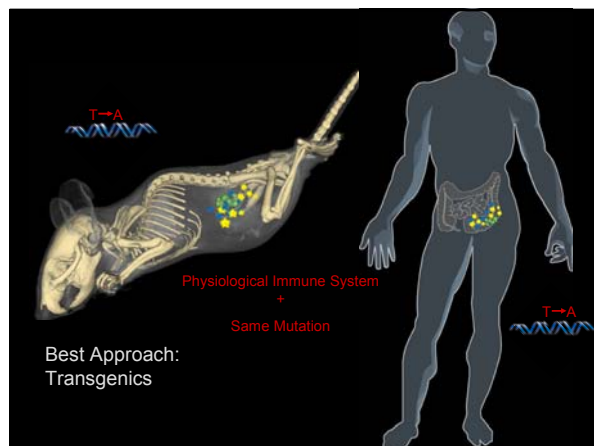
Better Orthotopic Technique ?

This is the place

Engineered Synthetic Matrix



building the better mouse...



Gene Targeting started in Utah and disseminated widely



Genentech
IN BUSINESS FOR LIFE

AVEO
PHARMACEUTICALS

NOVARTIS

Alveolar Rhabdomyosarcoma

Considerations for a Preclinical Model



Initiation (First Hits)

Pax3:Fkhr and Fkhr loss (65 – 70%)
Pax7:Fkhr and Fkhr loss (10 – 15%)

Common Alterations in Tumors (Second Hits)

MycN overexpression (43 – 60%)
CDKN2A (Ink4a/ARF) (30%)
p53 LOH (25%)
Igf2 LOI (22 – 100%)
Her2/neu (11 %)
Mdm2 amplification (8%)

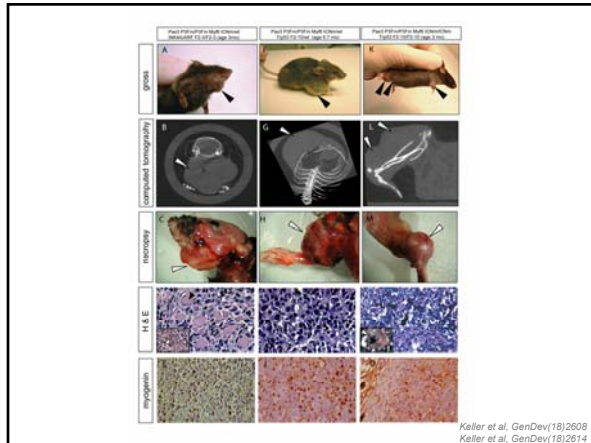
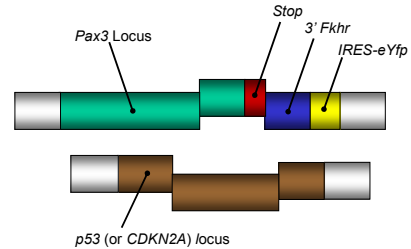
Arndt & Crist, 1999
 Other references...

The Conditional Mouse Model

Pax3:Fkhr On

(p53 Off)

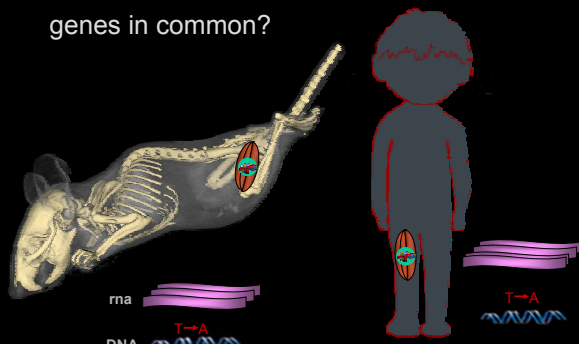
with Time- & Tissue Specificity



Keller et al. GenDev(18)2608
 Keller et al. GenDev(18)2614

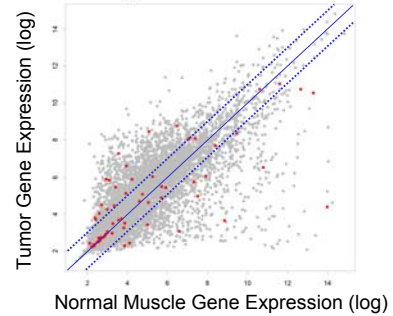
**What are potential
 therapeutic targets?**

Altered or mutated
 genes in common?



Is the previous literature informative (n=28) ?

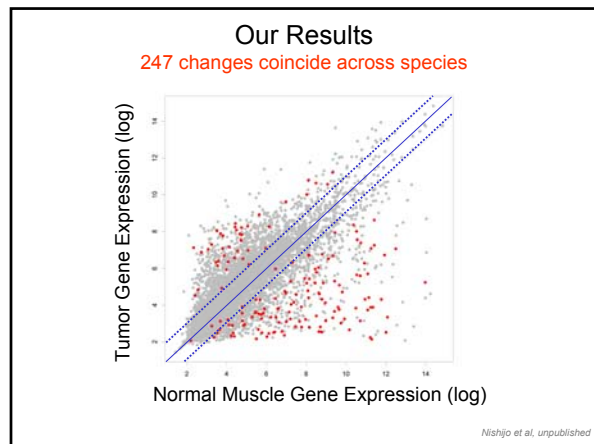
answer: to some extent (41%)



Pubmed ID (n = 28)

10579537
10557309
11607823
11863357
12122099
10571843
11863357
10537044
11489344
10557309
14996733
16728016
16157701
11735247
11735247
9706874
16213703
8985098
8769435
9824109
11863357
10700864
9632796
15120841
14204789
11171995
11863357

Nishijo et al. unpublished



Driving Biological Problem:

Understand Disease Progression

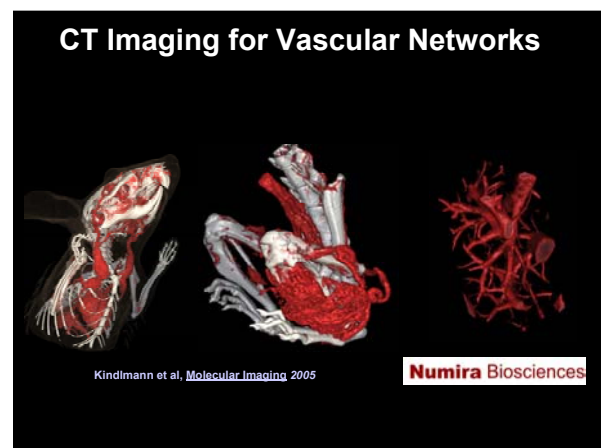
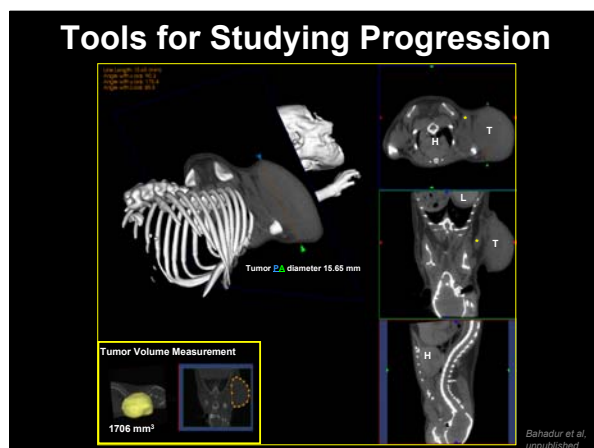
Imaging plays a critical role

www.sci.utah.edu www.visual-influence.com

Preclinical Tools: microCT & Optical

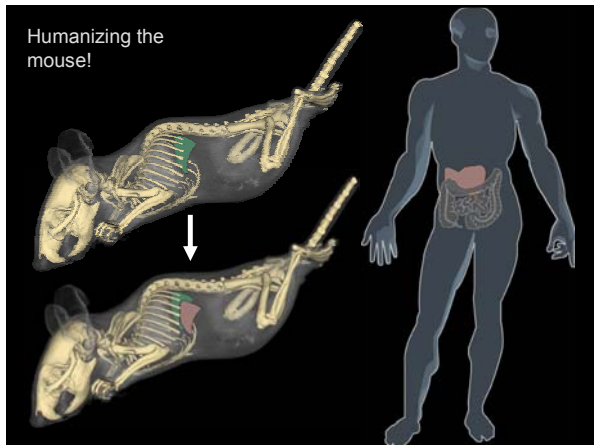
Volumetric Cone Beam
 80 keVp (fixed anode with tungsten target source)
 3500 x 1750 progressive readout CCD
 27 – 93 μ m resolution
 2 minute to 2+ hour acquisition time (21-24 min typical)
 Multi-processor rapid reconstruction cluster

Xenogen IVIS-200
 - Luminescence
 - Fluorescence

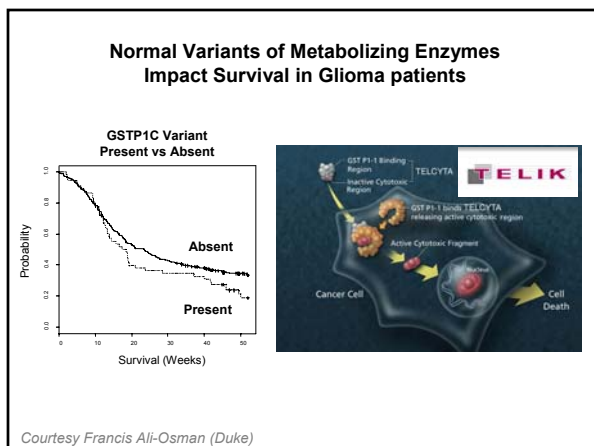




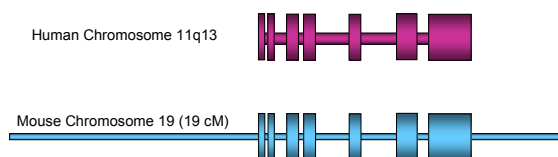
***What about differential
drug metabolism?***



a genetic solution?



Humanizing the GSTP1 Gene



Courtesy Francis Ali-Osman (Duke)

***Effective therapy,
but safe for unborn children?***

Why Utah?

Legacy in Human Genetics
Birthplace of Genetic Engineering
World Class Imaging Experts
Leadership

http://www.istockphoto.com/utahak_hong_kong/Three-Panoramas_Zion-National-Park_Utah.jpg



- [Keller Lab](http://www.sarcomalab.org) (www.sarcomalab.org)
- [Eri Taniguchi](#), [Koichi Nishijo](#)
- Omar Rivera, Sergio Vasquez
- Ali Bahadur, Isabel Wu
- Mandy McCleish, Andrea Rodriguez

- [Numira Biosciences](#)
- [Michael Beeuwsaert](#), [Ali Bahadur](#)

- [Capeocchi Lab](#)
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